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**Benzothiazole and stilbene derivatives as promising PET myelin radiotracers
for multiple sclerosis.**

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We thank Matias-Guiu and collaborators for their interesting comments regarding our recent article entitled “Dynamic imaging of individual remyelination profiles in MS”

(1). We had previously showed that both stilbene (2) and benzothiazole derivatives (3) could be applied to image myelin by PET in the CNS. The proof of concept clinical study we have performed indicates that this imaging approach is relevant in the context of multiple sclerosis to quantify myelin loss and repair, an objective that remained a major unmet need in this disease.

The interpretation of our results should not be limited to the context of acute clinical relapses, as the occurrence of an acute clinical relapse within the month before the baseline visit was one of the exclusion criteria for this study. However, all included patients presented a relapsing-remitting form of the disease (RRMS), with at least one gadolinium-enhancing lesion on the baseline MRI scan; this hallmark was hypothesized to be associated with ongoing, more active demyelination, hence with more dynamic endogenous remyelination that might be detected by PET.

Interestingly, Matias-Guiu and collaborators, using the stilbene derivative ^{18}F -florbetaben and a semi-quantitative approach, found a lower uptake in the progressive types of MS compared to RRMS, suggesting that disease progression may be associated with a persistent and cumulative process of myelin loss in the white matter (4).

The key remaining question is whether the individual remyelination profiles that were detected using ^{11}C -PIB PET have the potential to influence the long-term disease evolution. The population investigated had a 7.45 years mean disease duration, and the remyelination profiles were highly correlated with disability. In particular, a strong

correlation was found between the index of dynamic remyelination and the MS severity scale scores, that take into account the disease duration: this suggests that remyelination significantly influenced the accrual of medium-term disability during the RRMS phase. In order to establish the relationship with disability in the long-term, it will be necessary to further follow-up subjects, and to develop similar longitudinal studies in the later stages of the disease, especially over the course of progressive MS.

The uptake of the tracer in inflammatory conditions has been questioned, and in the context of cerebral amyloid angiopathy Carmona-Iragui et al (5) described a milder amyloid uptake in swollen areas. Contrasting with this finding, we showed a milder uptake reduction in gadolinium enhancing inflammatory lesions compared to overall T2 lesions. Therefore in MS, which is a non-amyloid disease, the inflammatory component does not seem to negatively bias the estimation of the myelin bound fraction. Furthermore, any bias linked to active lesions was minimized, as only 4% of the T2 lesional volume analysed by Bodini et al (1) was made of gadolinium enhancing lesions.

Finally we carefully quantified the ^{11}C -PIB binding in the normal appearing white matter of patients and found no difference with the white matter of control subjects. This contrasts with the report of Matias-Guiu et al that described a reduced uptake in the NAWM, a difference that could be explained by the inclusion of progressive patients in their cohort (7 among 12 patients). It would be of potential clinical interest to use the level of tracer binding the NAWM to discriminate RRMS from progressive MS. However, some methodological issues may have influenced Matias-Guiu's

findings. Firstly, in their study, only 3 subjects were included as healthy controls.

Secondly, Matias-Guiu's study was not conducted with dynamic acquisitions, as only static standardized uptake values (SUVs) were employed to measure ^{18}F -florbetaben uptake: this could represent a limit in the interpretation of the results, as it has been well shown for ^{11}C -PIB that using SUVs leads to a higher inter-subject variability and less reproducibility (6). Finally, in our study, peri-lesional regions were excluded from the NAWM analysis, as ^{11}C -PIB binding in those regions was significantly reduced compared to NAWM. It would be therefore of great interest to confirm Matias-Guiu's results after the exclusion of perilesional regions from the NAWM

Overall the application to MS of PET imaging with either stilbene or benzothiazole derivatives, especially those that may be labelled with fluorine-18, is indeed a promising emerging field of research that may extend the investigations to larger cohorts and improve our understanding of the disease physiopathology. Ultimately, this approach will allow the evaluation of candidate drugs aimed at promoting remyelination.

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